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EXAMINER
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ART UNIT 183 PAPER NUMBER 8
DATE MAILED: 08/26/91

For a complete explanation of the responses to this action, see the explanation of the action in the enclosed letter to the applicant.

☒ This application has been examined ☒ Responsive to AMENDMENT 8 communication filed on 5/31/91 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|---|
| 1. <input type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input type="checkbox"/> Notice re Patent Drawing, PTO-948. |
| 3. <input checked="" type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449. | 4. <input type="checkbox"/> Notice of Informal Patent Application, Form PTO-152 |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474. | 6. <input type="checkbox"/> _____ |

Part II SUMMARY OF ACTION

1. ☒ Claims 1-51 are pending in the application.
Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-51 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

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PTOL-326 (Rev. 9-89)

EXAMINER'S ACTION

In Amendment A filed May 31, 1991, Applicant's provisional election with traverse of Group I, claims
5 1 - 20 and 42 - 50, and further election of the methyl-
phosphonate species defined by the new claim 51 is
acknowledged. The restriction and election of species
10 requirement was defined in the written restriction
mailed April 1, 1991 (Paper No. 2).

After thorough consideration of the applicant's
traversal of the restriction and election requirements,
the examiner has rescinded all restriction and election
20 requirements. An action on the merits of claims 1 - 51
is presented below.

25 The following is a quotation of the appropriate
paragraphs of 35 U.S.C. § 102 that form the basis for the
rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

30 (b) the invention was patented or described in a printed
publication in this or a foreign country or in public use
or on sale in this country, more than one year prior to
the date of application for patent in the United States.

Claims 1 - 4, 8, 12 - 14, 19 - 23, 27 - 28, 31 - 33,
35 and 38 - 51 are rejected under 35 U.S.C. § 102(b) as being
anticipated by Miller et al. (Biochimie 67:769 - 776, 1985).
Miller et al. discloses oligonucleotides possessing methyl-
phosphonate linkages that inhibits the functioning of RNA.
Oligomers possessing all or predominately all methyl-
40 phosphonate groups read on the applicant's broad generic
claims using functional language to define the oligomers.

Claims 1 - 4, 12 - 14, 19, 21 - 23, 31 - 33, 38,
41, and 42 - 50 are rejected under 35 U.S.C. § 102(b) as
being anticipated by Matsukura et al. (PNAS 84: 7706-7710).
Matsukura et al. discloses oligomers with phosphorothioate
5 modified linkages. These oligomers were resistant to
nuclease digestion and were able to inhibit the functioning
of RNA.

10 The following is a quotation of 35 U.S.C. § 103 which
forms the basis for all obviousness rejections set forth in this
Office action:

15 A patent may not be obtained though the invention is not
identically disclosed or described as set forth in section
102 of this title, if the differences between the subject
matter sought to be patented and the prior art are such that
the subject matter as a whole would have been obvious at the
time the invention was made to a person having ordinary
skill in the art to which said subject matter pertains.
Patentability shall not be negated by the manner in which
the invention was made.

20 Subject matter developed by another person, which qualifies
as prior art only under subsection (f) or (g) of section 102
of this title, shall not preclude patentability under this
section where the subject matter and the claimed invention
were, at the time the invention was made, owned by the same
25 person or subject to an obligation of assignment to the same
person.

Claims 1 - 51 are rejected under 35 U.S.C. 103 as being
unpatentable over Sarin et al. (PNAS 85:7448-7451) in view
of Dash et al. (PNAS 84:7896-7900). Sarin et al. teaches
30 that oligonucleotides possessing methylphosphonate linkages
are biologically active and inhibit HIV expression. Further-
more, Sarin et al. teaches that oligomers possessing phosphoro-
thioate, phosphoramidate, or methylphosphonate linkages

all possessed the ability to inhibit HIV.

Dash et al. disclose that complementary antisense oligomers promote the degradation of target mRNA molecules and that this inhibition is irreversible.

5 Consequently, it would have been obvious to the person of ordinary skill in the art at the time of the invention to make and use antisense oligomers possessing modified linkages known to be resistant to nucleases for the purpose of inhibiting a specific target RNA and further promoting its degradation
10 by RNase H. The need to optimize both the hybridization of an oligomer to a RNA sequence and its resistance to nucleases is well recognized by the art at the time of the invention.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

15 The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use
20 the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description and failing to teach adequately how to make and/or
25 use the invention, i.e. failing to provide an enabling disclosure.

The specification is not enabling for all M's, N's, and B's defined by the generic claims. The breadth of the

claims is so great as to place an undue burden of experimentation upon the person of ordinary skill wanting to make and use the invention. There are hundreds of thousands of possible "modified nucleotides" that fall within the generic claims. However, the specifications exemplify one the methylphosphonate modification. The disclosure lacks guidance through the thousands of possibilities. While the applicant has provided RNase and nuclease screening assays, the burden of making and the screening so many is undue. For instance, which modified bases confer endo- or exonuclease resistance at N, M or B?

In addition, the applicant has not documented that ethyl, propyl and butylphosphonates are not so bulky as to interfere with proper hybridization to the RNA and RNase H activity as well. The bulkiness of these larger alkyl groups creates reasonable doubt that these potential RNA inhibitors will actually work.

Claims 1 - 51 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 1 - 51 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and 21 are so vague, indefinite, and confusing as to be nearly meaningless. The compound of claims 1 and 21 are termed a "modified nucleotide." It is not clear whether this is intended to mean an "oligonucleotide analog" or not. The three generic structures containing M, N, and B as variables are confusing. The claims are indefinite because the precise structure and attachment of these moieties to one another is not specified. Is N attached to M or B via the phosphodiester linkage or not? If N is attached to M or B via the phosphodiester linkage, is it through the 3'- or 5'-position? Both M and B are defined functionally instead of structurally. M is any nucleic acid that confers endonuclease resistance on the said "modified nucleotide." B is any moiety that confers exonuclease resistance to the terminus. Finally, the three generic formulas are vague because there is no indication which end is the 5'- and 3'-terminus.

Claim 3 continues the indefinite functional language by limiting the "modified nucleotide" to those capable of conferring RNase sensitivity to the RNA.

Claim 7 is indefinite because it fails to define specifically the location of the methyl group(s) attached to the bases.

The following two indefinite phrases are used repeatedly throughout the claims: "directly or indirectly attached" and "modified or unmodified." These phrases are vague because

they do not specify the particular type of structural
modification or attachment that fulfills the functional
5 limitations.

The method claims 21 - 39 have the same vague and indefinite
deficiencies as claims 1 - 20 but with additional problems
10 The method of inhibiting RNA is indefinite because it does
not specify the concentration of the inhibitor, the method
15 of delivery (added to media or injected into cell, or location
of the RNA (either intracellular or isolated)).

Claim 40 is indefinite because it fails to specify the
20 criteria for selecting the nucleotide compound having appropriate
resistance to nuclease activity. There are no reaction
25 conditions for the nuclease digestions and also no indication
concerning the extent of digestion that establishes that a
compound is or is not sufficiently resistant to function
30 as an RNA inhibitor.

Claim 41 is vague for the same reasons that claim 1 and 21
35 are indefinite. Furthermore, there is no regimen, dosage and
schedule, provided for treating a human or animal. The RNA
to be inhibited is not specified either.
40

Claims 42 - 50 are even more vague and indefinite than
claims 1 - 20 because of the functional language that is
45 intended to supplant structural definition:

"at least 1 exonuclease and endonuclease resistant
component"

50 "capable of specifically binding with a nucleic acid

sequence of interest to inhibit the function thereof"

"when complexed with a complementary RNA, confers
RNAse H sensitivity upon the RNA"

5

No claim is allowed.

10 Papers related to this application may be submitted
to Group 180 by facsimile transmission. Papers should
be faxed to Group 180 via the PTO Fax Center located in
Crystal Mall 1. The faxing of such papers must conform
with the notice published in the Official Gazette, 1096
OG 30 (November 15, 1989). The CM1 Fax Center number is
15 (703) 308-4227.

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Any inquiry concerning this communication or earlier
communications from the examiner should be directed to Examiner
Kunz whose telephone number is (703) 308-3995.

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M.K.
Gary L. Kunz:glk
August 25, 1991

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SUPERVISORY PATENT EXAMINER
ART UNIT 183

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